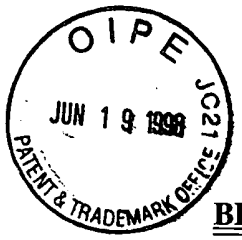
#21
Coffin
7/21/98



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:
Dennis E. HALLAHAN *et al.*

Serial No.: 08/540,343

Filed: October 6, 1995

For: METHODS AND COMPOSITIONS FOR VIRAL ENHANCEMENT OF CELL KILLING

§
§
§ Examiner: S. Priebe
§
§ Group Art Unit: 1632
§
§ Atty. Dkt: ARCD:194/HYL
§
§
§

CERTIFICATE OF MAILING
37 C.F.R 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

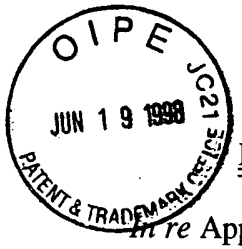
6/15/98
Date

Signature

REPLY BRIEF

Table of Contents

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Dennis E. HALLAHAN *et al.*	§	
	§	Examiner: S. Priebe
Serial No.: 08/540,343	§	
	§	Group Art Unit: 1632
Filed: October 6, 1995	§	
	§	Atty. Dkt: ARCD:194/HYL
For: METHODS AND COMPOSITIONS FOR VIRAL ENHANCEMENT OF CELL KILLING	§	

REPLY BRIEF

BOX AF
Hon. Asst. Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Examiner's Answer mailed on April 14, 1998, regarding the above-captioned application. This reply is due on June 14, 1997. Included with this filing is a request and corresponding fee for oral argument. Should appellants' check be missing or deemed deficient, or should other fees be deemed due, the Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Account No. 01-2508/ARCD:194/HYL.

I. FORMALITIES

The examiner has indicated that the Brief on Appeal contained no statement regarding related appeals of inteferences. This is not correct. The Brief clearly stated at page 2 that there were no related appeals or inteferences. The examiner has indicated that the amendments after final have been entered but there is an error in claim 38. This error will be rectified at such time as allowable subject matter is conceded.

II. REPLY

Turning to the Answer, the following points constitute new grounds of argument that are to be addressed in this Reply.

First, the examiner now admits equivalence (a) between HSV-1 and HSV-2 and (b) between the various serotypes of human adenoviruses, in the treatment of cancers as set forth in the specification. However, for the first time, the examiner now brings into question the ***sufficiency*** of the animal model described in the examples. This rather dramatic shift in basis for the rejection is neither well-founded in scientific reasoning nor does it derive from a proper reading of the controlling legal precedent.

In this regard, appellants direct the examiner to *In re Krimmel*, 130 USPQ 215 (CCPA 1961), in which the CCPA admitted "a demonstration that a compound has desirable or beneficial properties ... in experimental animals does not necessarily mean that the compound will have the same properties when used in humans." *Krimmel* at 219. Nonetheless, the Court

also stated that "With this information in mind, we hold that when an applicant for a patent has alleged ... that a new and unobvious chemical compound exhibits some useful pharmaceutical property ... by statistically significant tests with 'standard experimental animals,' sufficient statutory utility has been presented."[1, 2] *Id.*

The examiner argues that the exemplified tumor models are insufficient establish a correlation to treatment of ***all*** cancers in all mammals. However, appellants point out that mouse models have been sanctioned for testing the efficacy of human cancer therapies since the early 1960's. *See In re Krimmel, supra; In re Hartop,* 135 USPQ 419 (CCPA 1962)*; In re Bergel & Stock,* 130 USPQ 206 (CCPA 1961)*; In re Ross & Davies,* 134 USPQ 321 (CCPA 1962)*; and In re Westphal & Domagk,* 139 USPQ 378 (BPAI 1962). Against this considerable battery of precedent, the examiner offers nothing except to note that these mice used lack immune function. However, in this case, the ***presence*** of an immune system would ***confound*** the results by possibly adding an element of immune function to the anti-tumor effect. The animal models used in the present examples rely ***only*** on the treatment given - virus plus radiation - to achieve their results. Thus, the immunoincompetent model is the best model that can be provided.

Also, the argument against animal models appears to be premised on the notion that the present invention is subject to unpredictabilities associated with "gene therapy." However, as

[1] Any argument that the present rejection is based on §112, first paragraph, not §101, is beside the point, since the rationale for the rejections are identical - that the invention will not work as claimed.
[2] See also, *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985) ("Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.").

pointed out in prior responses, this invention does ***not*** rely on gene therapy for its effect. It merely requires the ***infection*** of cells *in vivo* by herpesvirus or adenovius -- something that is known to occur very easily -- and ***treatment*** using radiation, which also is well established. Thus, the balance of the examiner's discussion of Orkin, Lafont, Culver, Wilson and Marshall is off the mark. Whatever those papers may say about problems with genetic therapies (difficulties in delivering genes, difficulties with sustained expression, difficulties with immune responses), those concerns simply are not relevant here.[3]

It also should be pointed out that the standards for acceptance of a given therapy, in the scientific versus patent context, are quite distinct. Scientists are loath to overstate their successes fearing that their peers will view the disclosure as self-ingratiating. Further, scientists are trained to be critical thinkers and to view advances with some degree of circumspection. However, it has been made clear that establishing a clinic-ready protocol is not necessary for gaining patent protection.[4]

Second, the examiner now alleges that the primary difficulty with claims reciting brain or breast cancer is that these terms only define the ***location*** of the tumor and say nothing about their biology or their susceptibility to this kind of therapy. This is not true, however, and the examiner himself acknowledges this fact. "In general, the claims broadly encompass ... a variety of ***different***

[3] To highlight inappropriate nature of the rejection, one need only note the reference to Wilson and Marshall where it is stated that "the actual vectors - how we are gong to practice our trade - haven't been discovered yet." Answer at page 9. The "vectors" at issue here are viruses already in existence, adapted by centuries of selection to do precisely what is required of them in this context -- infect cells.

[4] The PTO's reviewing court also noted that even if a compound is ultimately shown to be "without value in the treatment of humans," the mere teaching that a compound exhibits ***some*** desirable property in an animal model "has made a significant and useful contribution to the art ...." *Krimmel* at 219.

tumor cell types originating from brain or breast tissue." Answer at page 5 (emphasis added). This representation corresponds with the art stated definition of cancer types by the ***tissue of origin***, and not necessarily the incidental location of the tumor.

Further, the examiner's line of reasoning in attacking the scope of the claims, with respect to tumor types, is based upon the same flawed reasoning as discussed above. Conceding that "HSV and Ad5 are able to infect a wide variety of cell types *in vitro* and presumably when cultured cells are implanted in a foreign, immune-compromised host," the examiner states that the underlying concern is "the ... recognized ... problems inherent in extrapolation from results obtained with animal models to cancer treatment in humans." However, as explained in the preceding comments, there is no valid reason why the mouse model data presented herein would not be considered as providing sufficient enablement for the claimed invention. Again, it must be reiterated (a) that there is adequate legal precedent for using mice to predict tumor therapy in humans, (b) that the cited literature does not argue that animal models are without value, only that they are not 100% predictive of efficacy, and (c) that the present invention does not involve gene therapy *per se*. In sum, the additional attack on tumor types is flawed as well.

Third, the examiner has stated that there is no correlation of doses to modes of administration or tumor size. Again, the examiner seems focused on pointing out what is missing from the specification, and not stating why that is a defect with regard to enablement. It cannot seriously be argued that providing specific doses for a given route is outside the ability of the skilled artisan to ascertain. Put another way, the examiner would appear to argue that determining

the exact operative dose of adenovirus or herpesvirus, for use according to the present invention, would be considered a separate patentable invention even facing the present disclosure as prior art -- in effect, the skilled artisan is being forced to exercise an inventive undertaking even when faced with the present disclosure. Appellants cannot believe that the examiner, when faced with this scenario, would not reject such particular doses as "clearly obvious" or "mere routine optimizations" of the present invention. Again, appellants advance is identifying and exploiting the cooperative activity of viral infection and radiation, a fact completely unheralded in the art.[5] Determining the precise operating parameters of these methods is something that can be left to the skilled artisan, without any legal detriment.

[5] *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980) ("Knowledge of the pharmacological activity of any compound is obviously beneficial to the public ....").

III. SUMMARY

In light of the foregoing remarks, it again is respectfully submitted that the appealed claims are enabled. Therefore, reversal of the rejection under 35 U.S.C. §112, first paragraph by the Board is respectfully requested.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642

Attorney for Appellant

ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, Texas 77210-4433
(512) 418-3000

Date: 6/15/98

APPENDIX 1: PENDING CLAIMS

8. The method according to claim 13, wherein the tumor cell is a human tumor cell.

10. The method according to claim 8, wherein the human tumor cell is a brain cancer cell.

11. The method according to claim 8, wherein the human tumor cell is a breast cancer cell.

13. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, a herpes simplex virus and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

15. The method according to claim 13, wherein the herpes simplex virus is HSV-1.

18. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a herpes simplex virus and (ii) ionizing radiation, wherein the combination of herpes simplex virus infection and radiation is more effective than ionizing radiation alone.

19. The method according to claim 18, wherein the composition comprises from about 10^8 to about 10^{10} herpesvirus particles.

20. The method according to claim 18, wherein the administering is by means of an oral or intravenous route.

21. The method according to claim 18, wherein the tumor is brain tumor or breast tumor.

22. The method according to claim 18, wherein the mammal is a human.

23. A method of killing a tumor cell comprising the steps of:

(a) contacting said tumor cell with a herpes simplex virus; and
(b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said herpes simplex virus.

24. The method according to claim 23, wherein the herpes simplex virus is HSV-1.

25. The method according to claim 13, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said herpes simplex virus.

26. The method according to claim 13, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

27. The method according to claim 13, wherein the tumor is a brain tumor or a breast tumor.

35. The method according to claim 46, wherein the tumor cell is a human tumor cell.

36. The method according to claim 35, wherein the human tumor cell is a brain cancer cell.

37. The method according to claim 35, wherein the human tumor cell is a breast cancer cell.

38. The method according to claim 46, wherein tumor the cell is located within an animal, and the adenovirus is administered to the animal in a pharmaceutically acceptable form.

39. The method according to claim 46, wherein the tumor cell is exposed to X-irradiation, γ-irradiation, or β-irradiation.

40. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, an adenovirus lacking an exogenous therapeutic gene and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

41. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a adenovirus lacking an exogenous therapeutic gene and (ii) ionizing radiation, wherein the combination of adenovirus infection and radiation is more effective than ionizing radiation alone.

42. The method according to claim 41, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

43. The method according to claim 41, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

44. The method according to claim 41, wherein the tumor is brain tumor or breast tumor.

45. The method according to claim 41, wherein the mammal is a human.

46. A method of killing a tumor cell comprising the steps of:

a) contacting said tumor cell with an adenovirus lacking an exogenous therapeutic gene; and

b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said adenovirus.

47. The method according to claim 46, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said adenovirus.

48. The method according to claim 46, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

49. The method according to claim 46, wherein the tumor cell is a brain tumor cell or a breast tumor cell.

50. The method according to claim 46, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

51. The method of claim 40, wherein said adenovirus is Ad5.

52. The method of claim 41, wherein said adenovirus is Ad5.

53. The method of claim 46, wherein said adenovirus is Ad5.

54. The method of claim 41, wherein said composition is administered intravenously.

55. The method of claim 55, wherein said composition comprises from about 10^8 to about 10^{11} adenovirus particles.